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RESEARCH

Effects of the perimenopausal period on the course of heart failure

Perimenopozal dönemin kalp yetersizliği seyrine etkileri

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Abstract

Purpose: It is known that the decrease in estrogen level in women's life has negative effects on the cardiovascular system. In this study, it was aimed to elucidate the changes in the clinical status and treatment requirement of patients with heart failure (HF) during the menopausal transition period.

Materials and Methods: A total of 26 patients followed up in the HF outpatient clinic between 2015–2020 were included in this retrospective, single-center study. Demographic data of the patients, New York Heart Association class, echocardiographic findings, routine biochemical parameters and HF signs, symptoms and therapies were examined. Data at the beginning of the menopause period and after 12 months were compared.

Results: At the end of the 12-month follow-up, a statistically significant increase was found in the daily dose of furosemide (50.5 mg/day vs. 72.4 mg/day). While the mean heart rate of the patients was 80.4±20.1 beats/min at the beginning, it was 69.3±10.1 beats/min in the control visit. Echocardiographically measured left ventricular (LV) systolic diameters of the patients were significantly increased compared to baseline in the control visit (41.2±7.4 mm vs 45.8±7.0 mm,).

Conclusion: The menopausal period caused an increase in the need for treatment in patients followed up with HF. Therefore, in evaluation of the patients with HF, it would be a useful approach to question the menopausal status in detail and to follow the patients more closely during the menopausal transition period.

Keywords: Estrogen; heart failure; menopause

Öz

Amaç: Kadın yaşamında östrojen seviyesindeki düşüşün kardiyovasküler sistem üzerinde olumsuz etkileri olduğu bilinmektedir. Bu çalışmada, kalp yetersizliği (KY) olan hastaların menopoza geçiş döneminde klinik durumlarındaki değişikliklerin ve tedavi gereksinimlerinin aydınlatılması amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif, tek merkezli çalışmaya 2015-2020 yılları arasında KY polikliniğinde takip edilen toplam 26 hasta dahil edildi. Hastaların demografik verileri, New York Heart Association fonksiyonel sınıfı, ekokardiyografik bulguları, rutin biyokimyasal parametreleri ile KY belirti, semptom ve tedavileri incelendi. Menopoz döneminin başlangıcındaki ve 12 ay sonraki veriler karşılaştırıldı.

Bulgular: 12 aylık takip sonunda, kullanılan günlük furosemide dozunda (50,5 mg/gün vs. 72,4 mg/gün) istatistiksel olarak anlamlı bir artış bulundu. Hastaların ortalama kalp hızı başlangıçta 80,4±20,1 atım/dk iken, 12 aylık takip sonunda 69,3±10,1 atım/dk idi. Hastaların ekokardiyografik olarak ölçülen sol ventrikül (LV) sistolik çapları, kontrol vizitinde başlangıca göre önemli ölçüde arttı (41,2±7,4 vs. 45,8±7,0 mm).

Sonuç: Çalışmamızda KY ile takip edilen hastalarda, menopozal dönemin tedavi ihtiyacında artışa neden olduğu belirlendi. Bu nedenle KY hastalarının değerlendirilmesinde menopozal durumun ayrıntılı olarak sorgulanması ve menopoza geçiş döneminde hastaların daha yakından takip edilmesi yararlı bir yaklaşım olacaktır.

Anahtar kelimeler: Kalp yetersizliği, menopoz, östrojen

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INTRODUCTION

Heart failure (HF) is a clinical syndrome that occurs due to functional and/or structural abnormalities in the myocardial structure and may present with unique symptoms and signs[1]. Heart failure is a problem affecting approximately 60 million people worldwide and is considered as a global epidemic. Although it is known that the prevalence of HF increases with age, there are differences between male and female patients[2]. Gender differences have also been defined in terms of epidemiology, etiology, pathophysiology and prognosis in patients with heart failure[3]. These differences between the sexes are attributed to the protective effect of estrogen[4].

Menopause is a process characterized by physiological changes affecting various organs and systems, especially the cardiovascular system, and is defined as the permanent termination of menstruation due to the loss of ovarian activity[5]. Although menopause is accepted as one of the physiological processes of women's life, not a disease, it is clear that it facilitates an enviroment susceptible to various diseases and reduces the quality of life. Even though the menopausal transition is not officially recognized as a risk factor for cardiovascular disease (CVD) in the guidelines, it is known that the decrease in estrogen level has negative effects on the cardiovascular system[6]. Estrogen exerts positive effects on the cardiovascular system either directly through genomic effects or indirectly through different mechanisms such as nitric oxide production, prevention of apoptosis in vascular cells, suppression of cytokines and the renin-angiotensin system (RAS)[7].

Menopause and the changes that occur in the body during this period are inevitable. What is important in this process is how ready the individual is for menopause and the changes it brings. However, in the presence of a syndrome that affects the whole body, such as HF, the changes caused by menopause can be more devastating. Conditions such as RAS activation resulting from decreased estrogen, increased aldosterone and sodium levels, water retention due to increased insulin levels may cause clinical deterioration in people with HF[6]. Knowing the changes that may occur during the menopause process in women with HF and optimizing the treatment accordingly will provide a significant improvement in the quality of life and expectations of the patients.

Therefore, in our study, it was aimed to elucidate the changes in the clinical status and treatment requirement of patients with HF during the menopausal transition period.

MATERIALS AND METHODS

Sample

A total of 26 patients followed up in the HF outpatient clinic between 2015–2020 were included in this retrospective, single-center, cross-sectional, observational study with the purpose of screening HF patients in the peri-menopausal period. Ethics Committee Approval was received from Health Sciences University Antalya Training and Research Hospital Ethics Committee (Approval date: 02.09.2021, No: 13/17). The study complied with the Declaration of Helsinki and informed consent has been obtained from all participants.

In this study, when α=0.05, β=0.20, 1-β=0.80, it was decided to include 25 individuals in the study and the power of the test was found to be 0.80892.

Female patients aged between 40–60 years, with left ventricular ejection fraction (LVEF) ≤50%, with last menstrual history data, and at least one year of regular follow-up (at least every three months routine control) were enrolled within the scope of this research. Patients who did not have last menstrual period data, had a known malignancy history, had a history of early surgical menopause, and had used hormone replacement therapy in the perimenopausal period were excluded from this research.

During the enrollment period 1260 consecutive patients with follow-up records in the HF outpatient clinic were screened. Of these patients, 351 were women and a total of 26 patients, out of 91 female patients aged 40 – 60 years, who met the inclusion criteria, were included in the study (Figure 1).

Procedure

Demographic data of patients, etiology of HF, presence of comorbidities such as concomitant hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease, New York Heart Association (NYHA) functional class, physical examination findings (height, weight, pulse, blood pressure), HF symptoms and signs, echocardiographic findings (LVEF, left ventricular systolic and diastolic diameters, left atrium size)

routine biochemical parameters (hemogram, sodium, potassium, creatine, troponin, N-terminal–pro-brain natriuretic peptide [NT-proBNP]), blood glucose, aspartate aminotransferase, alanine aminotransferase) values have been obtained.

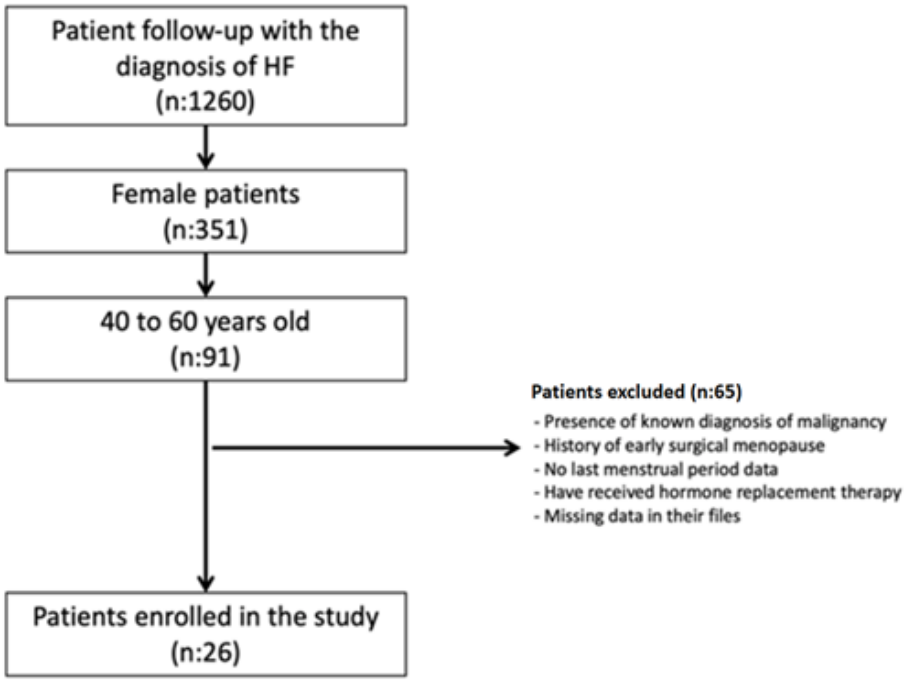

Figure 1. Flow chart of the study

All of the patients included in the study were patients who were followed up in the Heart Failure Outpatient Clinic of the Cardiology Department of Antalya Training and Research Hospital and had their files in the hospital registry system. In this heart failure outpatient clinic, patients are constantly followed by 3 cardiology specialists. The evaluations of the patients and the implementation of the study were also carried out by these cardiology specialists.

Electrocardiogram (ECG) (12-lead surface) findings, medications and doses used, were obtained from the hospital registry system. Transthoracic echocardiography (TTE) was performed in all patients with EPIQ 7 (Koninklijke Philips NV, Amsterdam, the Netherlands) echocardiography device and 1.5–4.5 MHz ultrasound probe by a cardiologist according to the American Society of Echocardiography Standards[8]. LVEF was measured by the Simpson method.

The last menstrual period data were confirmed by contacting the patients via phone interviews. In our study, the peri-menopausal period was determined as the time interval within one year from the last menstrual period in accordance with current definitions. Data collected at the beginning of the study were compared with the records at the 12th month controls. In addition, the patients were divided into two groups as hospitalized and non-hospitalized, and the differences between the groups were investigated.

Statistical analysis

The study parameters were recorded in the data collection form and statistical analyses were performed using IBM SPSS software version 25.0 (IBM Corp., Armonk, NY). Descriptive statistics are presented with frequency (%), mean±standard deviation, and median (min-max). In the statistical analysis, the conformity of the variables to the normal

distribution was examined by histogram graphics and the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to evaluate variables such as non-normally distributed (non-parametric) HF etiology, HF type, gender, presence of DM, HT, CRF, and COPD between the two groups. Changes in furosemide dose, heart rate, LV systolic diameter measurements were analyzed with the help of Wilcoxon test within the group and with the help of repeated measurement analysis between groups. Receiver operating characteristic (ROC) analysis was used to examine whether the parameters such as furosemide dose, creatinine, NT-proBNP and troponin that differed between the groups could predict hospitalization. Cases where the p value of <0.05 was considered as statistically significant.

RESULTS

The mean age of the 26 women participating in the study at the time of enrollment was 47.4±4.2 years. When the etiology of HF was examined, 8 (30.8%) patients had ischemic HF, while there were 18 (69.2%) patients with non-ischemic HF. The most common symptom at the time of admission was effort dyspnea and it was present in half of the patients. In addition, three patients had orthopnea complaints at the beginning and four patients with peripheral edema were detected. During the one-year follow-up period after inclusion in the study, four patients were hospitalized due to heart failure. The basic demographic characteristics of the patients were elaborated in Table 1.

Table 1. Baseline characteristics of the study population

Parameters		**N= 26**
Age at admission (year)		47.4±4.2
Body mass index (kg/m^2)		29.9±6.5
Follow-up period of heart failure (months)		21 (12-108)
Etiology of HF, n (%)	Ischemic cardiomyopathy	8 (30.8%)
	Non-ischemic cardiomyopathy	18 (69.2%)
Type of HF, n (%)	HF with reduced ejection fraction	24 (92.3%)
	HF with mildly reduced ejection fraction	1 (3.9%)
	HF with preserved ejection fraction	1 (3.9%)
Atrial fibrillation, n (%)		4 (15.4%)
Mild to severe valve disease, n (%)		12 (46.2%)
Hypertension, n (%)		13 (50%)
Diabetes mellitus, n (%)		12 (46.2%)
Chronic renal failure, n (%)		1 (3.9%)
Chronic obstructive pulmonary disease, n (%)		2 (7.7%)
Effort dyspnea, n (%)		13 (50.0%)
Orthopnea, n (%)		3 (11.5%)
Pretibial edema, n (%)		4 (15.4%)
Bendopnea time, (sec)		26 (5-40)
Number of hospitalizations due to HF, n (%)		4 (15.4%)
Angiotensin-converting enzyme inhibitors / Angiotensin receptor blockers, n (%)		20 (84.6%)
Angiotensin receptor-reprilysin inhibitor, n (%)		2 (7.7%)
Optimal Beta blocker therapy, n (%)		24 (92.3%)
Mineralocorticoid receptor antagonist (Spirinolactone), n (%)		21 (80.8%)
Loop diuretic (Furosemide), n (%)		20 (76.9%)

HF: Heart failure

No statistically significant difference was observed in the baseline and 12th month control body weight, blood pressure, mineralocorticoid receptor antagonist (MRA), LV diastolic diameter, LVEF, left atrium size, creatinine, sodium, potassium and troponin values. The majority of the patients included in the study were in NYHA Class I – II class and although this number decreased after 12 months of follow-up, but it was not statistically significant. While the mean NT-proBNP values were 1990.8±3839.5 pg/mL at baseline, it was 2410.6±4076.0 pg/mL in the control (Figure 2).

However, this increase in control examination values did not reach statistical significance (p=0.058). At the end of the 12-month follow-up, a statistically significant increase was found in the daily dose of furosemide (50.5 mg/day vs. 72.4 mg/day, p=0.034). While the mean heart rate of the patients was 80.4±20.1 beats/min at the beginning, it was 69.3±10.1 beats/min in the control visit. This decrease in heart rate was found to be statistically significant (p=0.008).

Echocardiographically measured LV systolic diameters of the patients were significantly increased compared to baseline in the control visit (41.2±7.4 mm vs 45.8±7.0 mm, p=0.002). The changes in the control data after the beginning of the menopausal period and after 12 months were denoted in Table 2.

Table 2. 12-month changes in patients' clinical, echocardiographic and laboratory values

Variables	Onset of menopause	End of perimenopausal period	P
Body weight (kg)	77.0±17.3	78.9±17.9	0.088
Systolic blood pressure (mmHg)	117.1±26.5	116.7±22.3	0.935
Diastolic blood pressure (mmHg)	71.5±15.1	71.9±12.3	0.985
Furosemide dose (mg/day)	50.5 (0 – 240.0)	72.4 (0 – 200.0)	0.034
MRA dose (mg/day)	19.2±12.9	16.8±15.4	0.366
Heart rate (beats/min)	80.4±20.1	69.3±10.1	0.008
LV diastolic diameter (mm)	54.2±7.1	52.7±7.0	0.278
LV systolic diameter (mm)	41.2±7.4	45.8±6.9	0.002
LV ejection fraction (%)	31.0±8.0	33.3±8.1	0.071
Left atrium diameter (mm)	42.4±6.6	43.1±6.6	0.488
Creatinine (mg/dl)	1.1±0.5	1.1±0.5	0.843
Potassium (mmol/L)	4.6±0.4	4.6±0.4	0.765
Sodium (mmol/L)	137.4±4.0	137.9±4.6	0.275
NT-proBNP (pg/mL)	1990.8 (21.0 - 19871.0)	2410.6 (16.4 - 17074.0)	0.058
Troponin (ng/L)	10.9 (3.0 – 29.0)	10.2 (3.0 – 33.0)	0.660
NYHA Class I-II, n (%)	22 (84.6%)	18 (69.2%)	0.705
Use of optimal B-blocker therapy, n(%)	24 (92.3%)	26 (100%)	0.162

LV: Left ventricular, MRA: Mineralocorticoid receptor antagonist, NT-proBNP: N-terminal–pro-brain natriuretic peptide, NYHA: New York Heart Association.

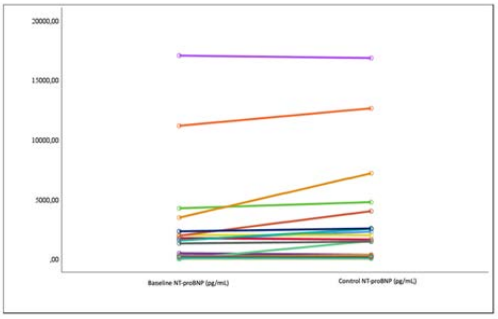

Figure 2. Change in N- terminal-pro-brain natriuretic peptide values in the 12- month follow-up of the patients

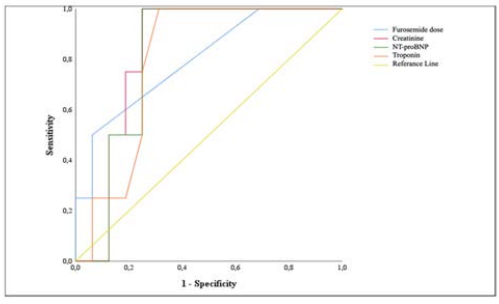

Figure 3. Predictors of hospitalization for heart failure in the perimenopausal period (ROC curve)

When the patients were divided into two groups as those who were hospitalized due to HF and those who did not, respectively; the initial daily dose of furosemide (38.1±24.3 mg vs. 100.0±95.2 mg, p=0.042), creatinine (1.0±0.5 mg/dL vs. 1.4±0.4 mg/dL p=0.019), NT-proBNP (1829.7±4143.2 pg/ml vs. 2876.8±1204.1 pg/ml, p=0.023) and troponin (9.6±7.8 ng/L vs. 18.5±9.6 ng/L, p=0.032) values were statistically significantly higher.

The predictability of furosemide dose, creatinine, NT-proBNP and troponin cut-off value values for hospitalization was examined (Table 3). The cut-off value for creatinine was found to be >1 mg/dL, with a sensitivity of 100% and a specificity of 81.82%. Additionally, 50% positive-predictive value (PPV) and 100% negative-predictive value (NPV) were obtained for this value (AUC, 0.828; 95% CI, 0.650-1.000; p=0.047) (Figure 3).

Table 3. Predictors of hospitalization for heart failure in the perimenopausal period

Variables	Area under the curve	Standard error	P	95% CI	
				Lower limit	Upper limit
Furosemide dosage (mg/day)	0.797	0.125	0.073	0.553	1.000
Creatinine (mg/dl)	0.828	0.091	0.047	0.650	1.000
NT-proBNP (pg/mL)	0.813	0.095	0.059	0.627	0.998
Troponin (ng/L)	0.797	0.099	0.073	0.603	0.990

CI: confidence interval, NT-proBNP: N-terminal–pro-brain natriuretic peptide

DISCUSSION

The main results of this study could be elaborated as an increase in the requirement for diuretic therapy in the peri-menopausal period of patients followed-up with HF. The presence of HF in patients did not affect the time to menopause, high creatinine in patients with HF in the peri-menopausal period was an independent predictor of HF hospitalization. Therefore, we suggest that closer follow-up of HF patients in the perimenopausal period may be beneficial.

Defining HF as a clinical syndrome and approaching its management holistically improves clinical outcomes. With the treatment modalities developed recently, life expectancy in HF patients has increased significantly[1]. However, there are many factors that negatively affect the course of the disease, such as age, HT, DM, and diet incompatibility[9,10]. It is known that the rational management of additional comorbidities in the follow-up of HF patients significantly improves the prognosis of the disease. With our study, the effect of menopause, which is an inevitable process of women's life, on the course of HF was investigated for the first time in the literature.

The mean age of menopause in our study was 47±4 years. In the western world, the average age of menopause is 51 years[11]. There is no significant change in the average age of menopause despite the prolonged life expectancy over the past years. In studies conducted in Turkiye, it has been shown that the mean age of menopause in women is 47 years[12,13]. The mean age at menopause found in our study was consistent with the data of our country. Although there are studies in the literature showing that early menopause increases the risk of HF, the answer to be given when this question is asked in reverse form is not clear. Although menopause is more likely to start earlier in people with a high Framingham risk score, it is not clear whether HF causes early menopause[14]. In our patient group, it was observed that HF present in the reproductive period did not affect the time to menopause.

There are significant data linking early menopause with an increased risk of CVD and death[6,15]. In the Framingham Study, the incidence of CVD was found to be higher in post-menopausal women around the age of forty compared to pre-menopausal women of the same age[14]. Similarly, Rahman et al. reported a 36% increase in the incidence of HF in women aged 40–45 years who entered natural menopause compared to menopausal women aged between 50–54 years[16].

These observations have prompted the hypothesis that estrogen is protective against CVDs[14]. Estrogen receptors are found on cardiac cells, including cardiac myocytes and fibroblasts. Estrogen exerts positive effects against hypertrophy, fibrosis and remodeling through genomic effects on these receptors. In addition, it prevents the deterioration of vascular endothelial functions with direct antioxidant effects

and effects on nitric oxide pathway. Estrogen level also has an effect on RAS, and plasma renin and angiotensin-converting enzyme (ACE) activity increases significantly in estrogen deficiency[17]. As a result, changes can be observed in the basic pathways that are the target of HF treatment. According to the results of our study, it can be deduced that these changes in compensatory mechanisms affect the treatment requirements of the patients. Therefore, the effects of hormonal changes occurring in the menopausal period on the pathophysiology and course of HF should be clearly demonstrated.

In the Multi-Ethnic Study of Atherosclerosis (MESA) research, cardiac remodeling in the post-menopausal period was evaluated with cardiac magnetic resonance imaging and it was observed that the left ventricular mass-volume ratio was higher in Chinese-American women with early menopause[18]. This condition has been associated with adverse cardiac remodeling. The fact that the increase in LV end-systolic diameter observed in our study was not accompanied by changes in end-diastolic and EF may be a result of the remodeling process due to decreased estrogen.

Recent epidemiological studies show that the prevalence of hypertension in pre-menopausal women increased to 19%, to 44% in perimenopausal women, and to 75% in post-menopausal women aged between 65–74 years[19]. Estrogen deficiency in post-menopausal women is associated with increased blood pressure due to increased ACE activity and sodium sensitivity. The prevalence of HT in women over 75 years of age is 85%, higher than in men of the same age[19]. In our study, the frequency of HT was found to be 50% in the patient group with a mean age of 47 years. Although Staessen et al., stated that a significant increase in blood pressure in the perimenopausal period, no increase in blood pressure was observed in our patient group[20]. Regular follow-up of patients and strict control of their treatments, may has prevented significant changes in blood pressure.

It is known that there is a tendency to gain weight in women during the menopausal period[21,22]. One of the most important reasons for weight gain could be elaborated as the increase in water and salt retention that occurs with the changing hormonal balance[23]. There was no statistically significant weight change in our patient group in the peri-menopausal period. However, there was a statistically significant increase in the daily dose of furosemide used by the patients during the 12-month period. It is known that increased insulin levels due to post-menopausal insulin resistance contribute to water and salt retention.

According to these results, one can say that an increase in the amounts of diuretics required by the patients during the menopause process can be determined by close follow-up, and their treatment can be regulated, thus preventing weight gain and thus congestion. Palpitation is a common complaint in the perimenopausal period and is considered as a sympathetic activation response to hormonal and vasomotor changes[24]. In our study, heart rate decreased significantly at 12-month follow-up. This showed that the detrimental effects of sympathetic activation during menopause can be prevented by optimal HF treatment in HF patients. Increasing the tolerated maximal beta-blocker dose in patients under HF follow-up may be the reason why we do not see the increase in heart rate during menopause in these patients.

The incidence of hospitalization in patients with HF varies between 12-45% in one year[25]. In our study, the rate of hospitalization at 1-year follow-up was found to be 15.4%, similar to the general population. Initial creatinine, troponin and NT-proBNP values of hospitalized patients were significantly higher. In a study by Smith et al., it was shown that worsening renal function was associated with adverse outcomes in patients hospitalized for HF. In the same study, it was determined that a creatinine value above 1 mg/dL was associated with the frequency of hospitalization[26]. In our study, it was seen that a creatinine value of 1 g/dL could predict HF hospitalization with high sensitivity and specificity. Estrogen deficiency in postmenopausal women is associated with increased angiotensin-converting enzyme activity and salt sensitivity, thus increased blood pressure. Uncontrolled progression of this process can result in decreased glomerular filtration and increased creatinine. Therefore, there is a need for larger studies examining the effect of decline in renal function in the menopausal period on the course of heart failure.

The most important limitations of this study could be attributed to its retrospective nature and relatively low number of sample size. Since the follow-up period was limited to 12 months, information about the late post-menopausal period could not be obtained. The majority of the patient group consists of heart failure with reduced ejection fraction. Based

on the HF classification according to LVEF, a homogeneous distribution did not occur. A clinical definition of menopause was made according to the date of the last menstrual period. In addition, since echocardiography measurements were not made by the same operator, measurement differences between operators may have occurred. No data could be obtained on premenopausal and/or postmenopausal serum estrogen and follicle-stimulating hormone levels, which provides more objective data. In our study, additional reproductive data of the patients were not available except for the age of menopause. This is another limitation of our study.

In conclusion, recognizing the conditions that may affect the prognosis in HF and intervening in a timely manner have positive effects on the outcomes. The number of studies evaluating the effect of menopause on hospitalization in HF is limited in the literature. In our study, it was determined that the perimenopausal period caused an increase in the need for treatment in patients followed up with HF. Although heart failure is seen in many patients in the postmenopausal period today, the data we obtained showed that there is a need for studies that will examine the premenopausal and menopausal transition periods more closely. Therefore, in the evaluation of a patient with HF, it would be a useful approach to question the menopausal status in detail and to follow the patients more closely during the menopausal transition period. Although the number of patients is small, our study may lead to prospective studies with a larger and longer follow-up period with its results.

Yazar Katkıları: Çalışma konsepti/Tasarımı: AŞ, ETŞ, GMYÖ, AG, MÖ; Veri toplama: AŞ, ETŞ, GMYÖ, AG; Veri analizi ve yorumlama: AŞ, ETŞ, GMYÖ, AG, MÖ; Yazı taslağı: AŞ, ETŞ, GMYÖ, AG, MÖ; İçeriğin eleştirel incelenmesi: AŞ, ETŞ, GMYÖ, AG, MÖ; Son onay ve sorumluluk: ETŞ, GMYÖ, AG, AŞ, MÖ; Teknik ve malzeme desteği: AŞ, ETŞ, GMY, AG; Süpervizyon: AŞ, ETŞ, GMYÖ, AG, MÖ; Fon sağlama (mevcut ise): yok.
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Hakem Değerlendirmesi: Dış bağımsız.
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Yazarın Notu: Bu çalışmaya katılan tüm katılımcılardan yazılı bilgilendirilmiş onam alınmıştır.

Author Contributions: Concept/Design : AŞ, ETŞ, GMYÖ, AG, MÖ; Data acquisition: AŞ, ETŞ, GMYÖ, AG; Data analysis and interpretation: AŞ, ETŞ, GMYÖ, AG, MÖ; Drafting manuscript: AŞ, ETŞ, GMYÖ, AG, MÖ; Critical revision of manuscript: AŞ, ETŞ, GMYÖ, AG, MÖ; Final approval and accountability: ETŞ, GMYÖ, AG, AŞ, MÖ; Technical or material support: AŞ, ETŞ, GMY, AG; Supervision: AŞ, ETŞ, GMYÖ, AG, MÖ; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained for this study from the Clinical Research Ethics Committee of Antalya Training and Research Hospital with the decision dated 02.09.2021 and numbered 13/17.
Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors declared no conflict of interest.
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